Virginia Department of Health
Brucellosis: Guidance for Healthcare Providers
Key Medical and Public Health Interventions after Identification of a Suspected Case

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1. Epidemiology

Brucellosis is a zoonotic bacterial disease caused by *Brucella*. Multiple *Brucella* spp. can infect humans: *B. abortus, B. melitensis, B. suis, B. canis, B. ceti and B. pinnepedalis*. *Brucella* spp. are designated as Category B agents (i.e., moderate ease of transmission and morbidity with a lower rate of mortality than Category A agents) and 3 species*, B. abortus*, *B. melitensis* and *B. suis*, are specifically designated as select agents which means that they could be developed as bioterrorism agents and that possession, use or transfer of these organisms requires registration with CDC or USDA.

Mammals are the natural reservoir for *Brucella.* Different *Brucell*a species are associated with different mammal reservoirs, as follows: *B. abortus* (mostly from cattle), *B. melitensis* (mostly from sheep and goats), *B. suis* (mostly from pigs), *B. canis* (mostly from dogs), *B. ceti* (from dolphins, porpoises, whales) and *B. pinnepedialis* (from seals, sea lions, walruses). Infection might occur in other animals, such as bison, elk, caribou, moose, wild hogs, or deer.

Although brucellosis occurs worldwide, it is more common in countries that do not have effective public health and domestic animal health programs. Areas currently listed as high risk include the following: the Mediterranean Basin (Portugal, Spain, France, Italy, Greece, Turkey and North Africa), Mexico, South and Central America, Eastern Europe, Asia, Africa, Caribbean and the Middle East.

In the United States, *B. melitensis* is the most commonly identified cause of brucellosis in humans. The primary sources of brucellosis are consumption of unpasteurized dairy products consumed in or imported from brucellosis-endemic areas, direct contact with meat or tissues of infected animals (e.g., blood, urine, vaginal discharges, aborted fetuses and placentas) and laboratory exposures to *Brucella* isolates. Auto-inoculation with animal brucellosis vaccines (e.g., injection or spraying into open wounds or eyes) has also been reported. Brucellosis is primarily an occupational hazard in the United States for slaughterhouse workers, meat-packing plant employees, farm workers,

veterinarians and laboratory workers. Brucellosis is 1 of the most frequently reported laboratory-acquired infections. Approximately 120 cases are reported annually in the United and 1 case is reported annually in Virginia.

2. Clinical Manifestations

The incubation period for brucellosis is highly variable, usually 5 to 60 days, but it can be as long as several months or more. The clinical spectrum of brucellosis is wide, ranging from asymptomatic infection to life-threatening disease. Patients might present with acute or chronic signs and symptoms. Signs and symptoms include fever that is constant or intermittent, chills, sweats, malaise, anorexia, headache, pain in muscles, joint, or back, fatigue, and weight loss and some patients might develop gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain). Lymphadenopathy, hepatomegaly, or splenomegaly might be identified upon physical examination. Chronic symptoms could include recurrent fever, chronic fatigue and depression. Localized infections occur in approximately 30% of cases and can affect any organ system, resulting in infections such as arthritis, swelling of the testicle and scrotum area (e.g., epididymo-orchitis),, swelling of the vertebrae (e.g., spondylitis), tissue abscess, or eye infections (e.g., uveitis). Neurologic involvement (e.g., meningitis) or cardiac involvement (e.g., endocarditis) are less common, but tend to be more severe. The case-fatality rate of untreated brucellosis is 2% or less and usually results from endocarditis associated with *B. melitensis* infection.

3. Specimen Collection and Laboratory Testing

Protocols for sentinel clinical laboratories are no longer posted on the CDC website. The American Society for Microbiology (ASM) has agreed to take the lead in the development and dissemination of sentinel laboratory information. The most current ASM guidelines for specimen collection and laboratory testing are available at http://www.asm.org/index.php/guidelines/sentinel-guidelines. For additional laboratory guidance, refer to the CDC Infectious Diseases Test Directory or CDC's Biosafety in Microbiological and Biomedical Laboratories (5th edition) (see References).

Laboratory personnel **must** be alerted if brucellosis is suspected so that appropriate precautions can be taken. All work on clinical specimens or isolates suspicious of *Brucella* should be performed in a biological safety cabinet and using biosafety level 3 (BSL-3) precautions. Because of the highly infectious nature of some *Brucella* species, consultation with the state public health laboratory, Division of Consolidated Laboratory Services (DCLS), is strongly recommended. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617. Sample collection instructions for testing at DCLS are shown in Table 1.

Table 1. Sample Collection and Testing Information for Suspected Brucellosis at DCLS and CDC*

Laboratory Test	Acceptable samples	Amount	Instructions
Brucella species identification and genotyping (at CDC)	Blood	10 cc	Use blood isolator tube or aerobic culture bottle. Ship at room temperature. Transport to lab within 16 hours.
	Serum	2–3 mL	Collect acute and convalescent serum (>14 days apart) in red top or tiger top tube. Remove serum and place in sterile tube. Acute and convalescent specimens can be shipped together (freeze acute specimen until convalescent specimen has been collected and is ready for shipment; ship both specimens on dry ice); if shipping separately, ship with cold packs.
	Abscess tissue: liver, spleen, or bone (testing conducted at CDC)	1 gram	Place in sterile container; moisten with sterile broth or saline. Ship as soon as possible with cold packs.
	Bone marrow (testing conducted at CDC)	1–2 cc	Ship in syringe with heparin. Remove needle and cap end. Ship at room temperature.
	Joint fluid (testing conducted at CDC)	1 mL	Place in sterile container. Ship as soon as possible with cold packs.
	Culture isolate	N/A	Send culture on an agar slant, not a plate. Agar slants should be shipped at room temperature.
Serology: *Brucella* microagglutination test (BMAT)	Serum	2–3 mL	Collect acute and convalescent serum (>14 days apart) in red top or tiger top tube. Remove serum and place in sterile tube. Acute and convalescent specimens can be shipped together (freeze acute specimen until convalescent specimen has been collected and is ready for shipment; ship both specimens on dry ice); if shipping separately, ship with cold packs. Note that serology is not available for *B. canis* or RB51.
Brucella spp. PCR	Whole blood, serum	0.5 – 1mL	Collect blood in purple top (EDTA). Ship with cold packs. Note that a negative test result does not rule out infection. PCR can detect *B. abortus*, *B. melitensis*, *B. suis* and *B. canis;* however, actual species identification is accomplished through culture confirmation.

*If brucellosis is suspected, notify the local health department immediately to discuss the case and laboratory testing (see www.vdh.virginia.gov/LHD/index.htm). Specimens should be sent to Division of Consolidated Laboratory Services (DCLS) after LHD has been consulted and testing has been approved by LHD/DCLS. The DCLS Emergency Duty Officer can be reached 24/7 at (804) 335-4617. In addition, the DCLS Blood and Body Fluid Submission Form should be completed with the appropriate test request (i.e., *Brucella* Microagglutination Test).

Presumptive identification criteria include:

- Colony morphology on sheep blood agar: *Brucella* species will appear as punctate colonies after 48 hours of incubation. Colonies are nonpigmented and nonhemolytic. All suspicious colony types should be examined by Gram stain and urea test.
- Gram stain morphology: *Brucella* species have a characteristic Gram stain morphology that is extremely helpful in differentiating them from other Gram-negative organisms. *Brucella* cells appear as tiny, faintly stained coccobacilli.
- Oxidase test (Kovac's modification) positive
- Urease test (Christensen's method) positive

Additional laboratory guidance is available in the Centers for Disease Control and Prevention (CDC) Brucellosis website available at http://www.cdc.gov/brucellosis/.

4. Diagnosis

The current CDC case definition for brucellosis is available at http://wwwn.cdc.gov/nndss/script/casedefDefault.aspx. Note that a case definition is a set of uniform criteria used to define a disease for public health surveillance. Case definitions enable public health to classify and count cases consistently across reporting jurisdictions, and should not be used by healthcare providers to determine how to meet an individual patient's health needs.

5. Treatment

Recommendations for brucellosis treatment of uncomplicated cases are summarized in Table 2. Key factors to consider for treatment are the following: 1) combination therapy is recommended because monotherapy can be associated with a higher rate of relapse and could potentially lead to drug resistance; 2) treatment regimens will depend on whether a localized infection (e.g., endocarditis, meningitis) or underlying condition that contraindicates certain antibiotics (i.e., pregnant women and children under the age of 8 years for whom tetracyclines are contraindicated) is present.

Table 2. Brucellosis treatment recommendations for uncomplicated cases*

Adults[†] • **Doxycycline** (100 mg twice daily, PO, for 6 weeks) and **rifampin** (600 to 900 mg/day, PO, for 6 weeks) or • **Doxycycline** (100 mg twice daily, PO, for 6 weeks) and **gentamicin** (5 mg/kg/day, IM, for 7 days) or • **Doxycycline** (100 mg twice daily, PO, for 6 weeks) and **streptomycin** (1g/day, IM, for 2 to 3 weeks)
Children[§] **For children ≥8 years:** • **Doxycycline** (2-4 mg/kg per day, maximum 200 mg/day, in 2 divided doses, PO, for a minimum of 6 weeks) or **tetracycline** (30-40 mg/kg per day, maximum 2 g/day, in 4 divided doses, PO, for a minimum of 6 weeks) and • **Rifampin**(15-20 mg/kg per day, maximum 600-900 mg/day, in 1 or 2 divided doses) **For children < 8 years (where tetracyclines are contraindicated)** • **Trimethoprim-sulfamethoxazole** (trimethoprim, 10 mg/kg per day, maximum 480 mg/day, PO, and sulfamethoxazole, 50 mg/kg per day, maximum 2.4 g/day, PO) divided in 2 doses for at least 4-6 weeks and **rifampin** (15-20 mg/kg per day, maximum 600-900 mg/day, in 1 or 2 divided doses)

*For additional information on dosing, please consult the package inserts. Uncomplicated case refers to a brucellosis infection that is relatively early in the bacteremic phase before focal organ involvement.

[†]Tetracyclines, including doxycycline, are not recommended for pregnant women. Both trimethoprim-sulfamethoxazole and rifampin appear to be safe drugs for treating brucellosis during pregnancy. Source: Young, EJ. *Brucella* Species. In: Mandell GL, Bennett JE, Dolin R, ed. *Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases*, 7th ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2010: 2924.

[§] Tetracyclines, including doxycycline, are not recommended for children aged less than 8 years. To decrease rate of relapse in children, combination therapy with a tetracycline (or trimethoprim-sulfamethoxazole if tetracyclines are contraindicated) and rifampin (15-20 mg/kg per day, maximum 600-900 mg/day, in 1 or 2 divided doses) is recommended. Source: In: Pickering LK, ed. *Red Book: 2012 Report of the Committee on Infectious Diseases, 29*th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:258.

6. Postexposure Prophylaxis

Recommendations for brucellosis postexposure prophylaxis (PEP) are provided in Table 3. Prophylaxis is not generally recommended following possible exposure to endemic disease. Prophylaxis recommendations based on type of exposure (e.g., laboratory exposure, exposure to live *Brucella* vaccine, or intentional exposure) are described below.

For exposures to *Brucella* in the laboratory, a risk assessment to determine if the exposure was high or low risk based on the activity and location should be conducted (see CDC Brucellosis: Assessing Laboratory Risk Level and PEP, available at http://www.cdc.gov/brucellosis/laboratories/risk-level.html). PEP is recommended for those with high-risk laboratory exposures and can be considered for those with low-risk laboratory exposures (Table 3). Persons with either a high- or low-risk exposure should be monitored for the development of signs or symptoms of brucellosis for 24 weeks from the time of last exposure. In addition, for those with high and low-risk exposures, serial serum specimens collected at 0, 6, 12, 18 and 24 weeks after exposure is recommended. If brucellosis occurs despite prophylaxis, a treatment regimen based on antimicrobial susceptibility results would need to be selected.

For exposures to live *Brucella* vaccine (e.g., *B. abortus* RB51), combination PEP therapy is recommended (Table 3). RB51, however, is resistant to rifampin in vitro, so rifampin is not recommended. In addition, serologic monitoring is not available for RB51 or *B. canis* exposures. All persons with live vaccine exposures should be actively monitored for fever for 4 weeks following last exposure and passively monitored for broader symptoms of brucellosis for 6 months following last exposure. If brucellosis occurs despite prophylaxis, treatment regimens would need to be selected based on antimicrobial susceptibility results.

For a *Brucella* exposure in which the organism was intentionally released as a biological weapon, prophylaxis regimens outlined in Table 3 for laboratory exposures should be followed because these guidelines cover aerosol-generating events.

Table 3. Postexposure prophylaxis (PEP) and monitoring recommendations for *Brucella* spp. exposures*

Exposure to *Brucella* spp. in a Laboratory*
• **Doxycycline** (100 mg twice daily, PO, for 3 weeks) and **rifampin** (600 mg once daily, PO, for 3 weeks) • All persons with high- or low-risk laboratory exposures should also be monitored for febrile illness for 6 months following last exposure and should undergo sequential serologic testing (e.g. 0, 6, 12, 18 and 24 weeks post exposure) using *Brucella* microagglutination testing available at DCLS.
Exposure to Live *Brucella* Vaccine among Veterinarians[†§]
• **Doxycycline** (100 mg twice daily, PO, for at least 21 days) and consider addition of **other suitable antimicrobials**

- All persons with high- or low-risk exposures should also be actively monitored for fever for 4 weeks following last exposure and passively monitored for broader symptoms of brucellosis for 6 months following last exposure.

*For additional information on dosing, please consult the package inserts. For persons with high-risk laboratory exposures, PEP is recommended; for persons with low-risk exposures in the laboratory, PEP might be considered· Trimethoprim-sulfamethoxazole should be considered for those patients with contraindications to doxycycline. Pregnant workers with high-risk exposures should consider PEP in consultation with their obstetricians. Persons with contraindications to rifampin should consult with their health care provider for alternative PEP. *B. abortus* RB51 is resistant to rifampin in vitro, so rifampin is not recommended for a laboratory exposure to RB51 vaccine. If brucellosis occurs despite prophylaxis, treatment regimens would need to be selected based on antimicrobial susceptibility results. Source: Centers for Disease Control and Prevention (CDC) Assessing Laboratory Risk Level and PEP at http://www.cdc.gov/brucellosis/laboratories/risk-level.html

†For pregnant women and those with contraindications to doxycycline, trimethoprim-sulfamethoxazole (160 mg/800mg, twice daily, PO, for at least 21 days) can be substituted for doxycycline. *B. abortus* RB51 is resistant to rifampin in vitro, so rifampin is not recommended for exposure to RB51 vaccine. Serologic monitoring is not available for RB51 or *B. canis* exposures. If brucellosis occurs despite prophylaxis, treatment regimens would need to be selected based on antimicrobial susceptibility results. Sources: 1) CDC Exposure to RB51: How to Reduce Risk of Infection at http://www.cdc.gov/brucellosis/veterinarians/rb51-reduce-risk.html; 2) Ashford, DA et al. Adverse events in humans associated with accidental exposure to the livestock brucellosis vaccine RB51. *Vaccine*. 2004; 22(25-26):3435-9.2004.

§For needle-stick injuries, local wound care and tetanus toxoid is also recommended (Source: Corbel, MJ, Food and Agriculture Organization of the United Nations, World Health Organization, World Organisation for Animal Health Available at http://www.who.int/csr/resources/publications/Brucellosis.pdf).

7. Vaccination

No vaccine is available for humans. A vaccine is used for cattle in areas heavily affected by brucellosis (not Virginia); however, the control strategy for cattle focuses on testing animals for infection and isolating and euthanizing infected herds.

8. Infection Control

In addition to standard precautions, contact precautions are indicated for patients with draining wounds.

9. Decontamination

Brucella is sensitive to exposure to heat and most disinfectants, but can survive in the environment for several months under optimum conditions, particularly those with high humidity, low temperatures and no sunlight.

10. Postmortem Practices

If brucellosis is suspected as a cause of death, the district Office of the Chief Medical Examiner should be immediately notified (see http://www.vdh.virginia.gov/medExam/ContactUs.htm). Consultation should occur regarding whether an autopsy should be conducted, parties responsible for conducting the autopsy, and proper personal protective procedures to follow.

11. Public Health Measures

- Suspected or confirmed brucellosis cases should be reported immediately to the local health department. See http://www.vdh.virginia.gov/LHD/index.htm.

- Laboratory specimens should be sent to the state public health laboratory (DCLS) for confirmation of agent and other studies after consultation and approval. The DCLS Emergency Services Officer can be reached 24 hours a day/7 days a week at (804) 335-4617.
- Designated public health authority should begin an epidemiologic investigation.
  - Collect detailed information from the patient to attempt to identify the source of the exposure (e.g., consumption of unpasteurized dairy products or exposure to infected animals).
  - Investigate contacts of the patient for compatible illness to investigate a potential common exposure.
  - Collect suspected food items (e.g., unpasteurized milk, soft cheeses, etc.) for possible testing. VDH's Office of Epidemiology will work with the Virginia Department of Agriculture and Consumer Services (VDACS) if commercially prepared food is implicated.
  - Notify VDACS if animal exposures are identified.
  - Implement control measures to prevent disease and additional exposures. For laboratorians or others potentially exposed who might have worked with the agent before identification as *Brucella* spp., postexposure prophylaxis and monitoring might be recommended based on a risk assessment.
  - VDH will work with the CDC, Federal Bureau of Investigation (FBI) and other state or federal agencies as necessary.

12. References and Resources

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